



**EUROPEAN PATENT APPLICATION**

Application number: 92111090.4

Int. Cl.<sup>5</sup>: **C07D 239/42, C07D 239/38,  
A61K 31/505**

Date of filing: 30.06.92

Priority: 01.07.91 JP 188015/91

Date of publication of application:  
07.01.93 Bulletin 93/01

Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU MC  
NL PT SE**

Applicant: **SHIONOGI SEIYAKU KABUSHIKI  
KAISHA**  
1-8, Doshomachi 3-chome Chuo-ku  
Osaka 541(JP)

Inventor: Hirai, Kentaro  
720, Uematsu-sho, Teramachidori,  
Matsubarasagaru  
Shimogyo-ku, Kyoto-shi, Kyoto(JP)  
Inventor: Ishiba, Teruyuki  
1-4-6, Kawazoe  
Takatsuki-shi, Osaka(JP)  
Inventor: Kolke, Haruo  
2-33, Koaza, Higashikawahara, Oaza, Hishida  
Seika-sho, Soraku-gun, Kyoto(JP)  
Inventor: Watanabe, Masamichi  
8-1-201, Uchidehama  
Otsu-shi, Shiga(JP)

Representative: **Vossius & Partner**  
Siebertstrasse 4 P.O. Box 86 07 67  
W-8000 München 86(DE)

**Pyrimidine derivatives as HMG-CoA reductase inhibitors.**

The compounds of the present invention inhibit the HMG-CoA reductase, and subsequently suppress the biosynthesis of cholesterol. And they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

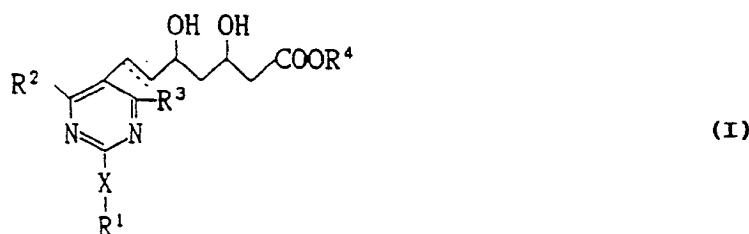
**EP 0 521 471 A1**

The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors

The first generation of drugs for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, are mevinolin (U.S. Pat. No. 4,231,938), pravastatin sodium (U.S. Pat. No. 4,346,227), and simvastatin (U.S. Pat. No. 4,444,784) which are fungal metabolites or chemical derivatives thereof. Recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (F.G. Kathawala et al, 8th Int'l Symp. on Atherosclerosis, Abstract Papers, p. 445, Rome (1988)) and BMV 22089 (GB Pat. No. 2,202,846) were developed as the second generation drugs.

The compounds of the present invention inhibit the HMG-CoA reductase, which plays a major role in the synthesis of cholesterol, and thus they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

The present invention relates to compounds of the formula (I):



wherein  $R^1$  is lower alkyl, aryl, or aralkyl, each of which may have one or more substituents;  $R^2$  and  $R^3$  each is independently hydrogen, lower alkyl, or aryl, and each of said lower alkyl and aryl may have one or more substituents;  $R^4$  is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a substituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone. This invention also provides a pharmaceutical composition comprising the same.

In the specification, the term "lower alkyl" refers to a straight, branched, or cyclic  $C_1$  to  $C_6$  alkyl, including methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, cyclo-pentyl, n-hexyl, and isohexyl and the like. Further, the lower alkyl may be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano. Halogen means fluorine, chlorine, bromine and iodine.

The term "aryl" refers to a  $C_6$  to  $C_{12}$  aromatic group including phenyl, tolyl, xylyl, biphenyl, naphthyl, and the like. The aryl may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano. Preferred aryl is phenyl substituted by 1 to 3 halogen atoms.

The term "aralkyl" refers to  $C_1$  to  $C_6$  lower alkyl substituted by  $C_6$  to  $C_{12}$  aromatic aryl group defined above. Examples are benzyl, phenethyl, phenylpropyl and the like, each of which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, cyano, and the like.

The term "a cation capable of forming a non-toxic pharmaceutically acceptable salt" refers to an alkali metal ion, an alkaline earth metal ion, or an ammonium ion. Examples of alkali metals are lithium, sodium, potassium, and cesium, and examples of alkaline earth metals are beryllium, magnesium, and calcium. Sodium and calcium are preferred.

Examples of "acyl" are formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, and isovaleryl.

In the term "imino which may have a substituent", preferred substituents are acyl, optionally substituted amino, and substituted sulfonyl.

The term "substituted amino as substituent" means an amino group substituted by sulfonyl and alkylsulfonyl. Examples are sulfonyl amino and methanesulfonyl amino.

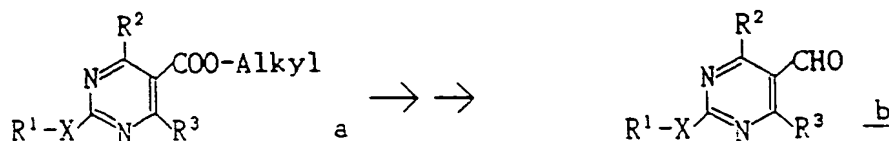
The term "substituted sulfonyl as substituent" means a sulfonyl group substituted by alkyl, amino, or alkylamino. Examples are methanesulfonyl, sulfamoyl, methylsulfamoyl, and N-dimethylsulfamoyl.

The compounds of the present invention can be prepared by the following method.

(1) The carboxylate group of the compound a is converted into the alcohol group by reduction in an appropriate inactive solvent such as THF, ether, and toluene in the presence of a reductant such as  $LiAlH_4$  and DIBAL-H. The reaction is performed at  $-70$  to  $50^\circ C$ , preferably at around room temperature, for 10 minutes to 10 hours, preferably for 30 minutes to 3 hours. Then the obtained alcohol is subjected to oxidation in an appropriate solvent such as methylene chloride in the presence of the oxidizing agent

such as TPAP/4-methyl-morpholin-N-oxide or pyridium chlorochromate to give the aldehyde compound b. The reaction is performed at 0-60 °C, preferably at around room temperature, for 10 minutes to 10 hours, preferably 30 minutes to 3 hours.

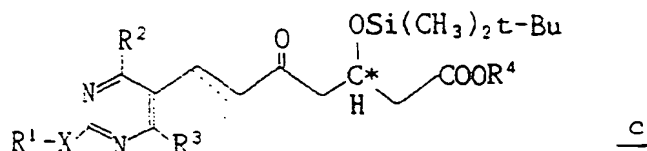
Compounds a and b have the following structure:



wherein R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> each has the same meaning as defined above, and Alkyl means lower alkyl.

(2) The obtained compound b is subjected to reaction with (3R)-or (3S)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanoic acid derivatives in an appropriate solvent such as acetonitrile, diethylether, tetrahydrofuran, and dimethylformamide to give the compound c. The reaction is performed for 1-30 hours, preferably for 10-15 hours under heating.

Compound c has the following structure:



wherein C\* represents an asymmetric carbon atom, the dotted line denotes the presence or absence of the double bond, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> each have the same meaning as defined above.

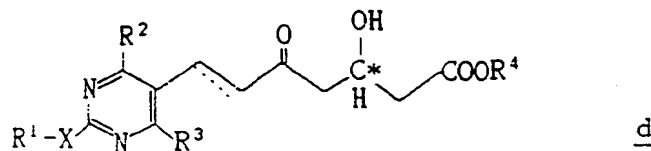
(3) The compound c is subjected to elimination of the tert-butyldimethylsilyl group in an appropriate organic solvent in the presence of a hydrogen halogenide to give the compound d.

Every sort of halogen can be used for hydrogen halogenide. Amongst all, hydrogen fluoride is preferred.

The same organic solvents as used in the step (2) may be employed. Acetonitrile is especially preferred.

The reaction is performed in a range of from 0 to 60 °C, preferably at room temperature, for 0.5-10 hours, preferably for 1-2 hours.

Compound d has the following structure:



wherein C\*, the dotted line, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> each have the same meaning as defined above.

(4) The compound d is reacted with diethylmethoxyborane and NaBH<sub>4</sub> in an alcohol-organic solvent mixture and subjected to column chromatography on silica gel to give the compound (I) (in the case where R<sup>4</sup> is lower alkyl). The reaction is performed at a temperature between -100 to 20 °C, preferably between -85 to -70 °C under cooling, for 10 minutes to 5 hours, preferably for 30 minutes to 2 hours.

Here, the alcohol includes methanol, ethanol, propanol, and butanol; and the organic solvent includes the same as in the step (3).

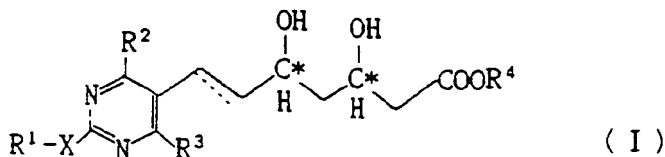
Further, if necessary, the obtained compound may be subjected to saponification with a solution of metallic hydroxide (R<sup>4</sup> : cation), and after the saponification, the reaction mixture is neutralized with an acid and extracted with an organic solvent (R<sup>4</sup> : hydrogen). The saponification is performed in a polar

solvent such as water, acetonitrile, dioxane, acetone, or a mixture thereof, preferably in the presence of a base, by a conventional method. The reaction is performed at 0 to 50 °C, preferably at around room temperature.

As the metallic hydroxide sodium hydroxide, potassium hydroxide, and their analogues may be used.

Acids which may be used include inorganic acids such as hydrochloric acid, sulfuric acid and the like.

The optically active compounds of the invention have the following structure (I):



wherein C\*, the dotted line, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> each has the same meaning as defined above.

Further, if necessary, the obtained compounds (I) are subjected to reflux under heating to give the corresponding lactones. Pharmaceutical compositions comprising the compounds of the present invention can be administered orally or parenterally. For example, the compound of the present invention may be orally administered in the form of tablets, powders, capsules, and granules, aqueous or oily suspension, or liquid form such as syrup or elixir, and parenterally in the form of aqueous or oily suspension.

These preparations can be prepared in a conventional manner by using excipients, binders, lubricants, aqueous or oily solubilizers, emulsifiers, suspending agents, and the like. Preservatives and stabilizers can be also used.

The dosages may vary with the administration route, age, weight, condition, and the kind of disease of the patients, but are usually 0.5-200 mg/day, preferably 1-100 mg/day for oral administration and 0.1-100 mg/day, preferably 0.5-50 mg/day for parenteral administration. They may be used in single or divided doses.

The present invention is illustrated by the following examples and reference examples, which are not to be considered as limiting.

The abbreviations used in examples and reference examples have the following meanings.

Me : methyl, Et : ethyl, i-Pr : isopropyl

t-Bu : tert-butyl, Ph : phenyl,

DMF : dimethylformamide, THF : tetrahydrofuran

DDQ : 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

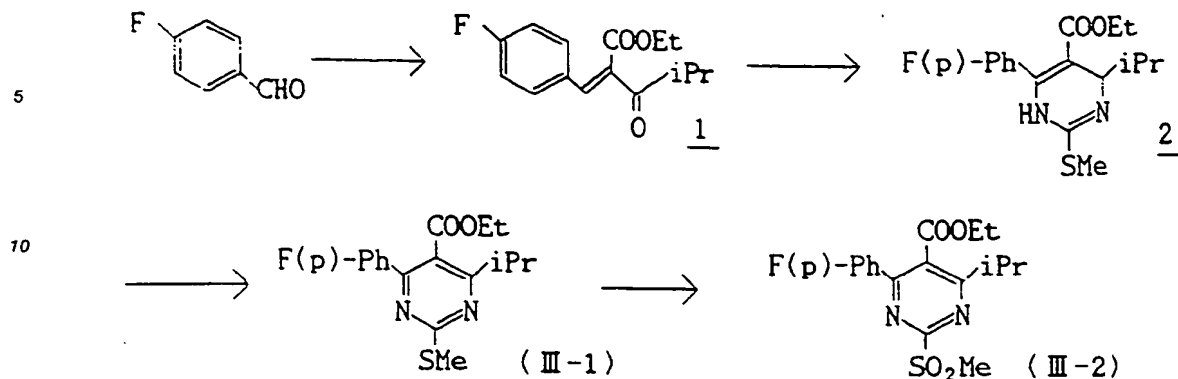
TPAP : tetrapropylammonium perruthenate

HMPA : hexamethylphosphoramide

DIBAL-H : diisobutylaluminum hydride

#### Reference Example 1

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylthiopyrimidine-5-carboxylate (III-1) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methyl-sulfonylpyrimidine-5-carboxylate (III-2)



p-Fluorobenzaldehyde (81.81 g) is reacted in the same manner as disclosed in the specification of JP Unexamined Pat. Publ. No. 61-40272 to give 151.0 g (Yield : 86.7 %) of the compound 1. Then the mixture of a solution of 44.68 g of the compound 1 in 65 ml of HMPA and 28.24 g of s-methylisourea hydrogen sulfate is stirred at 100 °C for 22 hours. Then the reaction mixture is extracted with ether, and washed with saturated sodium hydrogencarbonate and then with water. The organic layer is dried, and the solvent is distilled away. The obtained residue is subjected to column chromatography on silica gel to give 26.61 g (yield 46.8%) of the compound 2.

To a solution of the obtained compound 2 in 400 ml of benzene 21.64 g (0.095 mol) of DDQ is added and the mixture is stirred for 30 minutes. Then the mixture is subjected to column chromatography on silica gel to give 24.31 g (Yield : 91.9 %) of the compound (III-1).

NMR (CDCl<sub>3</sub>) δ :

1.10 (t, J = 7.3 Hz); 1.31 (d, J = 7.6 Hz); 2.61 (s, 3H); 3.18 (hept, J = 7.1 Hz); 4.18 (q, J = 7.2 Hz); 7.12 (m, 2H); 7.65 (m, 2H)

To a solution of 13.28 g (0.04 mmol) of the compound (III-1) in chloroform 17.98 g of m-chloroperbenzoic acid is added and the reaction mixture is stirred at room temperature. Then it is washed with sodium sulfate and then with saturated sodium hydrogencarbonate. The solution is dried, and the solvent is distilled away and washed with n-hexane to give 13.93 g (Yield : 95.7%) of the compound (III-2).

NMR (CDCl<sub>3</sub>) δ :

1.16 (t, J = 7.3 Hz); 1.37 (d, J = 7.6 Hz); 3.26 (hept, J = 7.1 Hz); 3.42 (s, 3H); 4.28 (q, 2H); 7.18 (m, 2H); 7.76 (m, 2H)

#### Reference Example 2

##### Another synthetic method of the compound (III-1)

To a solution of 200 mg (0.594 mmol) of the compound 2 in 5 ml of dichloromethane 0.5 g (6.10 equivalent) of potassium carbonate is added and 166 mg (1.1 equivalent) of iodine, and the mixture is stirred at room temperature for 2.5 hours. After the reaction, saturated sodium hydrogensulfite is added to the mixture which is then extracted with ether. The organic layer is washed with water and dried. The solvent is distilled off under reduced pressure to give 166 mg (Yield : 83.6%) of the compound (III-1) as resinous substance.

NMR (CDCl<sub>3</sub>) δ :

1.10 (t, 3H J = 7); 1.31 (d, 6H, J = 7); 2.61 (s, 3H); 3.17 (heptet, 1H, J = 7); 4.18 (q, 2H, J = 7); 7.07-7.17 (m, 2H); 7.61-7.69 (m, 2H)

#### Reference Example 3

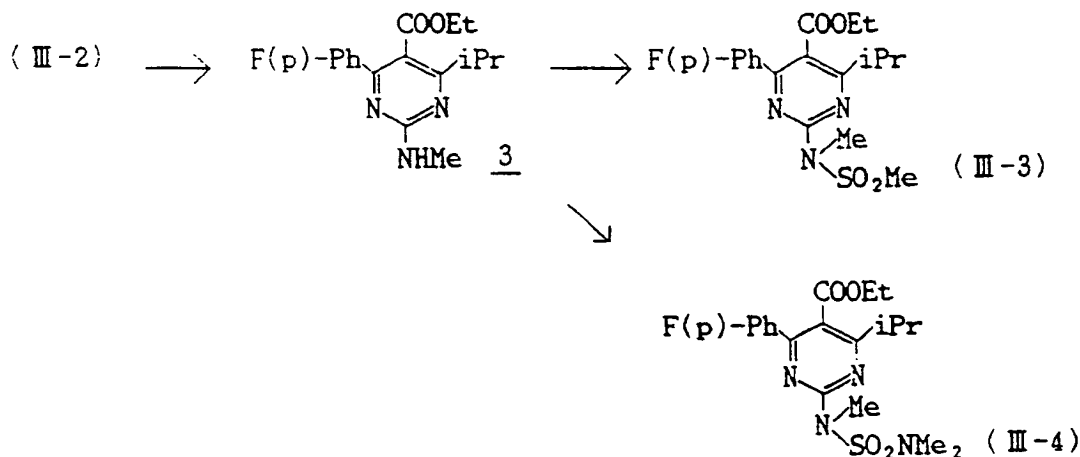
##### Another synthetic method of the compound (III-2)

To a solution of 1.0 g (2.97 mmol) of the compound 2 in 10 ml of acetone 1.5 g (9.48 mol) of potassium permanganate is added and the mixture is stirred at room temperature for 15 minutes. Acetic acid (1.0 ml) is

added thereto, and the mixture is stirred at room temperature for further 30 minutes and water is added thereto. The reaction mixture is extracted with ether, washed with saturated sodium hydrogen carbonate and saturated brine and dried over anhydrous magnesium sulfate. The solvent is distilled away under reduced pressure to give 1.07 g (2.94 mmol) (Yield : 99.1 %) of the compound (III-2) as crystals.

#### Reference Example 4

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-carboxylate (III-3) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-dimethylsulfonylamino)pyrimidine-5-carboxylate (III-4)



To a solution of 52.7 g (144 mmol) of the compound (III-2) in 500 ml of absolute ethanol solution of 71.9 ml of 5N methylamine in ethanol is added gradually under ice-cooling. The reaction mixture is warmed to room temperature, stirred for 1 hour and evaporated under reduced pressure. To the residue water is added and the mixture is extracted with ether, dried and evaporated under reduced pressure to give 46.9 g (Yield : 100%) of the compound 3. mp. 85-86 °C

Anal Calcd. (%) for C <sub>17</sub> H <sub>20</sub> N <sub>3</sub> FO <sub>2</sub>				
:	C,64.34;	H,6.35;	N,13.24;	F,5.99
Found:	C,64.42;	H,6.46;	N,13.30;	F,6.14

To a solution of 370 mg (1.213 mmol) of the compound 3 in 5 ml of DMF 60 mg of 60% NaH is added under ice-cooling and the reaction mixture is stirred for 30 minutes. Methanesulfonyl chloride 208 mg is added thereto, and the mixture is warmed to room temperature and stirred for 2 further hours. To the mixture ice-water is added and the mixture is extracted with ether. The organic layer is washed with water and dried. The solvent is evaporated under reduced pressure, and the resulting residue is washed with ether-n-pentane to give 322 mg (Yield: 57.6%) of the compound (III-3).

NMR (CDCl<sub>3</sub>)  $\delta$  :

1.10 (t, J = 7.3H); 1.32 (d, J = 7.6H); 3.24 (hept, J = 7.1H); 3.52 (s, 3H); 3.60 (s, 3N); 4.19 (q, J = 7.2H); 7.14 (m, 2H); 7.68 (m, 2H)

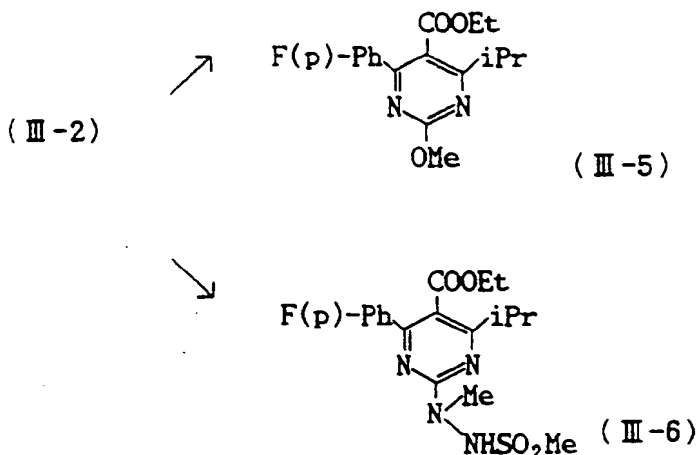
To a solution of 4.13 g (13.0 mmol) of the compound 3 in 40 ml of DMF 0.57 g of 60% NaH is added under ice-cooling, and the mixture is warmed to room temperature and stirred for 1 hour. After cooling again, dimethylsulfonyl chloride 2.43 g (16.9 mmol) is dropwise added thereto, and the mixture is stirred for 2.5 hours. To the mixture ice-water is added and the mixture is extracted with ether, washed with water, dried and evaporated under reduced pressure to distill off the ether. The resulting residue is washed with ether-hexane to give 4.10 g (Yield: 74.2%) of the compound (III-4). mp. 114-116 °C

Anal Calcd. (%) for C <sub>19</sub> H <sub>25</sub> N <sub>4</sub> SFO <sub>4</sub>				
	C,53.76;	H,5.94;	N,13.20;	F,4.48
Found :	C,53.74;	H,5.96;	N,13.19;	F,4.78

## Reference Example 5

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxypyrimidine-5-carboxylate (III-5) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-

N-methylsulfonylhydrazino)pyrimidine-5-carboxylate (III-6)



To a solution of 1.39 g (3.8 mmol) of the compound (III-2) in 60 ml of absolute methanol a solution of 0.41 g (7.6 mmol) of sodium methoxide is added under ice-cooling. The reaction mixture is gradually warmed to room temperature and stirred for 1 hour. The mixture is neutralized with acetic acid and extracted with ether. The organic layer is washed with sodium bicarbonate and then with water, dried and evaporated under reduced pressure to distill off the ether. The residue is subjected to column chromatography on silica gel to give 1.17 g (Yield : 96.7%) of the compound (III-5).

NMR (CDCl<sub>3</sub>) $\delta$  :

1.10 (t, 3H, J = 7Hz); 1.32 (d, 6H, J = 6.6Hz); 3.21 (m, 1H); 4.08 (s, 3H); 4.18 (q, 2H, J = 7Hz); 7.07-7.74 (m, 4H)

To a solution of 2.50 g (6.77 mmol) of the compound (III-2) in 50 ml of absolute ethanol 0.80 g (16.93 mmol) of methyl hydrazine is added under ice-cooling. The reaction mixture is warmed to room temperature and stirred for 2 hours and extracted with ether. The organic layer is washed with saturated brine and dried to distill off the solvent. To a mixture of 2.37 g of the thus obtained compound and a mixture of anhydrous THF and anhydrous pyridine 1.03 g (7.84 mmol) of methanesulfonyl chloride is added under ice-cooling. The reaction mixture is warmed to room temperature and stirred for 1.5 hours. To the mixture 3 ml of anhydrous pyridine and 1.53 g (11.65 mmol) of methanesulfonyl chloride are added and the mixture is stirred for 2 hours. To the reaction mixture ice-water is added and is then extracted with ether. The organic layer is washed with water and the resulting oily residue is subjected to column chromatography on silica gel to give 2.75 g (Yield : 94.0 %) of the compound (III-6).

NMR (CDCl<sub>3</sub>) $\delta$  :

1.08 (t, J = 7,3H); 1.29 (d, J = 7,6H); 2.96 (s, 3H); 3.24 (hept, J = 7,1H); 3.59 (s, 3H); 4.16 (q, J = 7,2H); 7.14 (m, 2H); 7.63 (m, 2H)

## Reference Example 6

Methyl (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate

(1) (3R)-3-(tert-butyldimethylsilyloxy)glutaric acid-1-((R)-(-)-mandelic acid ester<sup>\*1</sup> (65 g, 164 mmol) is dissolved in 60 ml of methanol. A solution of sodium methoxide in methanol (28% methanol 310 ml, 1.6 mol) is added dropwise thereto under a nitrogen atmosphere at 0 °C for 45 minutes at an internal temperature under 7 °C. The reaction mixture is stirred at 0 °C for 30 minutes and poured into a mixture of 150 ml of conc.HCl, 300 ml of water, and 500 ml of methylene chloride being stirred under ice-cooling. The organic layer is collected. The aqueous layer is extracted with 200 ml of methylene chloride, and each organic layer is washed with dil.HCl and then with brine. Each organic layer is collected and dried over anhydrous magnesium sulfate and evaporated to distill off the solvent to give the half ester compound.

<sup>1</sup>HNMR(CDCl<sub>3</sub>) $\delta$  :  
0.08 (s, 3H); 0.09 (s, 3H); 0.86 (s, 9H); 2.52-2.73 (m, 4H); 3.08 (s, 3H ); 4.55 (quint, 1H, J=6Hz)  
IR (CHCl<sub>3</sub>) : 2880, 1734, 1712, 1438, 1305, 1096, 836 cm<sup>-1</sup>  
[ $\alpha$ ]<sub>D</sub> = -5.0 $\pm$ 0.4 ° (C=1.04, 23.5 °C, CHCl<sub>3</sub>)  
Rf 0.32 (CHCl<sub>3</sub>/MeOH=9/1)

(2) To a solution of the thus obtained half ester compound in 10 ml of ether triethylamine and then ethyl chlorocarboxylate are added dropwise under nitrogen atmosphere at -78 °C. The resulting white suspension is stirred at 0 °C for 1 hour and cooled to -78 °C. The resulting precipitate is filtered off under nitrogen atmosphere and the filtrate is washed with 15 ml of ether. To a suspension of 1.29 g (3.6 mmol) of methyl bromide triphenylphosphonium in 5 ml of THF butyllithium (1.6M hexane, 2.25 ml, 3.6 mmol) is added dropwise under a nitrogen atmosphere at -78 °C. The reaction mixture is stirred at 0 °C for 1 hour and cooled to -78 °C and added dropwise to the solution of the thus obtained active ester compound in ether. The reaction mixture is washed with 5 ml of THF and stirred at 0 °C for 1 hour, and 10 ml of 5 % sodium hydrogencarbonate is added thereto. The reaction mixture is stirred for 5 minutes and extracted with ethyl acetate and the organic layer is separated and the remaining aqueous layer is extracted with ethyl acetate. Each organic layer is collected and washed with brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue is subjected to column chromatography on silica gel eluting with ether-ethyl acetate and crystallized from ether-hexane to give the objective compound.

<sup>1</sup>HNMR (CDCl<sub>3</sub>) $\delta$  :  
0.04 (s, 3H); 0.06 (s, 3H); 0.83 (s, 9H); 2.4-2.9 (m, 4H); 3.64 (s, 3H); 3.74 (d, 1H); 4.5-4.7 (m, 1H); 7.4-7.8 (m, 15H)  
IR (CHCl<sub>3</sub>) : 2880, 1730, 1528, 1437, 1250, 1106, 835 cm<sup>-1</sup>  
[ $\alpha$ ]<sub>D</sub> = 6.2 ° (C=1.27, 22.0 °C, CHCl<sub>3</sub>)  
mp. :77.5-78.5 °C, Rf=0.48 (CNCl<sub>3</sub>/MeOH=9/1)

Anal Calcd. (%) for C <sub>31</sub> H <sub>35</sub> O <sub>4</sub> PS			
: C, 69.63;	H,7.35;	P,5.79	
Found : C, 69.35;	H,7.35;	P,6.09	

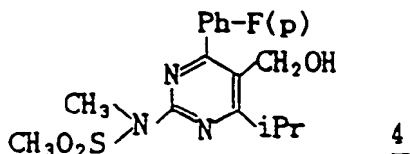
Example 1

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin-5-yl)]-(3R,5S)-dihydroxy-(E)-6-heptenate (Ia-1)

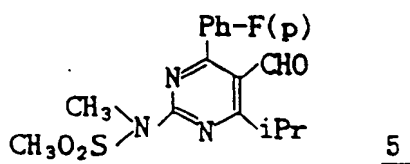
(1) To a solution of 322 mg of the compound (III-3) obtained in Reference Example 2 in 7 ml of anhydrous toluene 1.4 ml of DIBAL-H in 1.5M toluene is added dropwise at -74 °C. The reaction mixture is stirred for 1 hour and acetic acid is added thereto. The mixture is extracted with ether. The organic layer is washed with sodium bicarbonate and water, dried and then evaporated under reduced pressure to distill off ether. The obtained residue is subjected to column chromatography on silica gel, eluting with methylene chloride/ether (20/1) to give 277 mg (Yield : 96.1%) of [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonyl-amino)pyrimidin-5-yl]methanol 4.

\*1: This compound can be prepared by the method described on page 10 in the specification of KOKAI 2-250852.

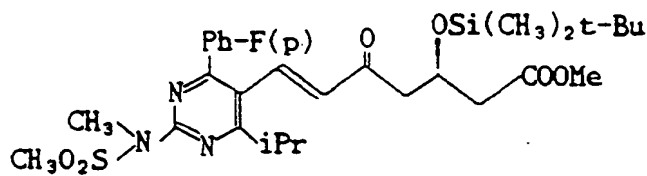




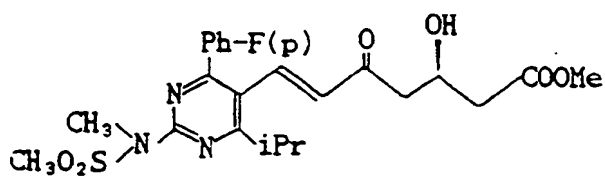
10 (2) A suspension of 277 mg of the thus obtained compound 4, 190 mg of 4-methylmorpholin-N-oxide, 6 mg of TPAP, 1.0 g of powder molecular sieve 4A, and 10 ml of methylene chloride is stirred for 2 hours. The insoluble matter is filtered off and two-thirds of the filtrate is distilled away under reduced pressure. The resulting residue is subjected to column chromatography on silica gel eluting with methylene chloride to give 196 mg (Yield : 71.2%) of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidinecarbaldehyde as crystals.



25 (3) A solution of 190 mg of the compound 5, 450 mg of methyl (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate (Reference Example 6), and 5 ml of acetonitrile is refluxed under beating for 14 hours and evaporated under reduced pressure to distill off acetonitrile. The resulting residue is subjected to column chromatography on silica gel eluting with methylene chloride to give 233 mg (Yield : 71.3%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-pyrimidin-5-yl]-(3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-(E)-6-heptenate 6 as a syrup.

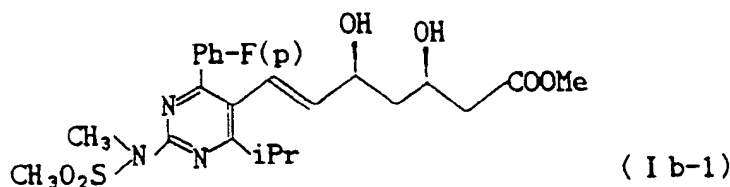


40 (4) To a solution of 16 g of the compound 6 in 100 ml of acetonitrile a solution of 48% hydrogen fluoride in 400 ml of acetonitrile (1:19) is added dropwise under ice-cooling, and the mixture is warmed to room temperature and stirred for 1.5 hours. The reaction mixture is neutralized with sodium bicarbonate and extracted with ether. The organic layer is washed with sodium chloride, dried and evaporated under reduced pressure to distill off ether to give 13 g (Yield : 100%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R)-3-hydroxy-5-oxo-(E)-6-heptenate 7 as a syrup.



(5) To a solution of 13 g of the compound 7 in 350 ml of anhydrous THF and 90 ml of methanol a

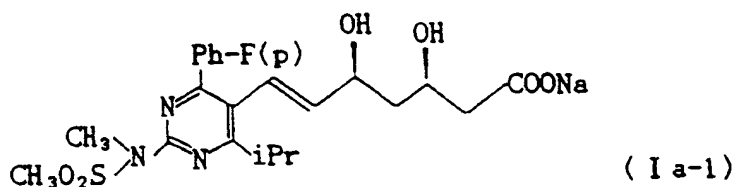
solution of 29.7 ml of 1M diethylmethoxyborane-THF is added at -78° C, and the mixture is stirred at the same temperature for 30 minutes. To the mixture 1.3 g of NaBH<sub>4</sub> is added and the mixture is stirred for 3 hours. Acetic acid (16 ml) is added thereto, and the mixture is adjusted to pH 8 with saturated sodium bicarbonate and extracted with ether. The organic layer is washed with water, dried and the ether is evaporated under reduced pressure. To the resulting residue methanol is added and the mixture is evaporated under reduced pressure for three times. The resulting residue is subjected to column chromatography on silica gel, eluting with methylene chloride/ether (3/1) to give 11.4 g (Yield : 85.2%) of methyl 7-[4-(4-fluorophenyl)-6-iso-propyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate as a syrup.



NMR (CDCl<sub>3</sub>) $\delta$  :

1.27 (d, J=7,6H); 1.53 (m, 2H); 2.47 (d, J=6,2H); 3.36 (hept, J=2H); 3.52 (s, 3H); 3.57 (s, 3H); 3.73 (s, 3H); 4.20 (m, 1H); 4.43 (m, 1H); 5.45 (dd, J=5,16, 1H); 6.64 (dd, J=2,16, 1H); 7.09 (m, 2H); 7.64 (m, 2H)

(6) To a solution of 11.4 g of the compound (Ib<sup>-1</sup>) in 160 ml of ethanol 223 ml of 0.1 N sodium hydroxide is added under ice-cooling. The reaction mixture is warmed to room temperature and stirred for 1 hour. The solvent is distilled off under reduced pressure, and ether is added to the resulting residue and the mixture is stirred to give 11.0 g (Yield : 95.0%) of the objective compound (Ia<sup>-1</sup>) as powdery crystals.



$[\alpha]_D = +18.9 \pm 0.6^\circ$  (C=1.012, 25.0° C, H<sub>2</sub>O)

NMR (CDCl<sub>3</sub>) $\delta$  :

1.24 (d, J=7,6H); 1.43 (m, 1H); 1.65 (m, 1H); 2.27 (dd, J=2,6,2H); 3.41 (hept, J=7,1H); 3.43 (s, 3H); 3.59 (s, 3H); 3.73 (m, 1H); 4.32 (m, 1H); 5.49 (dd, J=7,16, 1H); 6.62 (d, J=16,1H); 7.19 (m, 2H); 7.56 (m, 2H)

## Example 2

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-acetyl-N-methylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I<sup>a-2</sup>)

(1) Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylaminopyrimidine-5-carboxylate 3 (838 mg) obtained in Reference Example 4 is allowed to react in the same manner as in Example 1 (1) and (2) to give 157 mg of 4-(4-fluorophenyl)-6-isopropyl-2-methylaminopyrimidine-5-carbaldehyde.

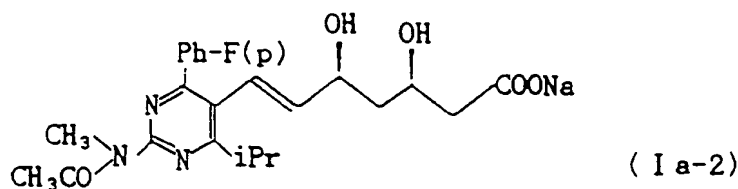
(2) A solution of 157 mg of the thus obtained aldehyde compound in 4ml of anhydrous DMF is reacted with 25 mg of 60 % NaH under ice-cooling for 30 minutes, 0.05 ml of acetylchloride is added thereto and the mixture is stirred for 1 hour. Ice is added to the mixture and extracted with ether. The organic layer is washed with water and dried and concentrated to distill off the solvent to give 167 mg (Yield : 93.4%) of 4-(4-fluorophenyl)-6-isopropyl-2-(N-acetyl-N-methylamino)-pyrimidine-5-carbaldehyde. The thus obtained aldehyde compound is reacted in the same manner as in Example 1 (3)-(5) to give methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-acetyl-N-methylaminopyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I

b-2).

NMR (CDCl<sub>3</sub>) $\delta$  :

1.27 (d, J=7,6H); 1.54 (m, 2H); 2.48 (d, J=6,2H); 2.52 (s, 3H); 3.39 (hept, J=7, 1H); 3.60 (s, 3H); 3.58 (brs, 1H); 3.74 (s, 3H); 4.21 (m, 1H); 4.48 (m, 1H); 5.50 (dd, J=5,16, 1H); 6.66 (dd, J=2,16); 7.11 (m, 2H); 7.61 (m, 2H)

(3) The thus obtained compound (I<sup>b-2</sup>) is reacted in the same manner as Example I (6) to give the objective compound (I<sup>a-2</sup>).

NMR (CDCl<sub>3</sub>) $\delta$  :

1.27 (d, J=7,6H); 1.57 (m, 2H); 2.17 (s, 3H); 2.27 (d, J=6,2H); 3.72 (s, 3H); 3.50 (hept, J=7, 1H); 3.70 (m, 1H); 4.35 (q, J=6,1H); 5.59 (dd, J=5,16, 1H); 6.54 (d, J=16, 1H); 7.24 (m, 2H); 7.59 (m, 2H)

Example 3-6

As starting material, each pyrimidine carboxylate (III) obtained in Reference Example 1-3 is reacted in the same manner as Example 1 or 2 to give the compounds(I<sup>b</sup>) and (I<sup>a</sup>). Their physical constants are shown in Table 1-3.

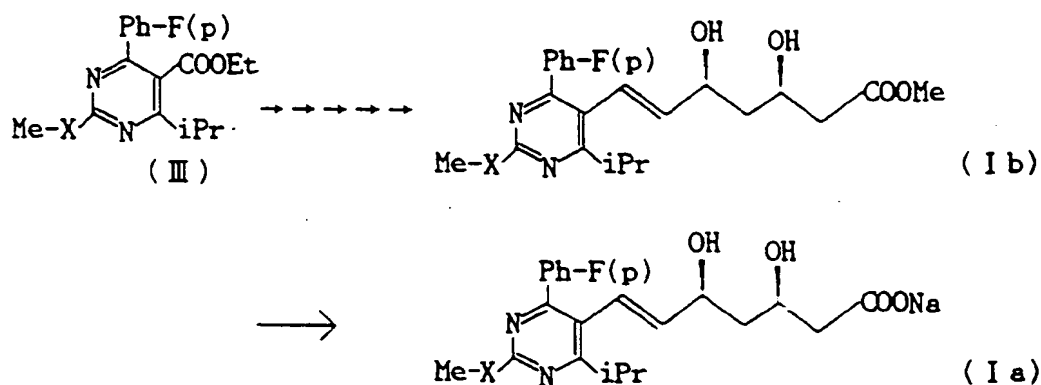


Table 1

Ex. No.	Starting material	Product NMR $\delta$
3	(III-1)	$I^{b-3}$ (X: S) Yield 96.0% ( $CDCl_3$ ) 1.26 (d, J = 7, 6H); 1.52 (m, 2H); 2.47 (d, J = 6, 2 H); 2.60 (s, 3H); 3.33 (hept, J = 7, 1H); 3.73 (s, 3H); 4.18 (m, 1H); 4.44 (m, 1H); 5.44 (dd, J = 5, 16, 1H); 6.60 (dd, J = 2, 16, 1H); 7.07 (m, 2H); 7.58 (m, 2H) $I^{a-3}$ (X: S) Yield 87.3% ( $D_2O$ ) 1.20 (d, J = 7, 6H); 1.47 (m, 1H); 1.61 (m, 1H); 2.26 (m, 2H); 2.54 (s, 3H); 3.36 (hept, J = 7, 1H); 3.71 (m, 1H); 4.29 (m, 1H); 5.43 (dd, J = 6, 16, 1H); 6.55 (d, J = 16, 1H); 7.16 (m, 2H); 7.47 (m, 2H)
4	(III-2)	$I^{b-4}$ (X: $SO_2$ ) : Yield 93.7% ( $CDCl_3$ ) 1.31 (d, J = 7, 6H); 1.52 (m, 2H); 2.48 (d, J = 6, 2H); 3.40 (s, 3H); 3.47 (hept, J = 7, 1H); 3.74 (s, 3H); 3.87 (brs, 1H); 4.23 (m, 1H); 4.49 (m, 1H); 5.59 (d, d, J = 5, 16H, 1H); 6.74 (d, d, J = 2, 16, 1H); 7.12 (m, 2H); 7.69 (m, 2H) $I^{a-4}$ (X: $SO_2$ ) : Yield 70.9% ( $D_2O$ ) 1.27 (d, d, J = 7, 2, 6H); 1.60 (m, 2H); 2.25 (J = 6, d, 2H); 3.44 (s, 3H); 3.51 (hept, J = 7, 1H); 3.70 (m, 1H); 4.33 (q, J = 6, 1H); 5.65 (d, d, J = 5, 16, 1H); 6.71 (d, J = 16, 1H); 7.23 (m, 2H); 7.60 7.60 (m, 2H)

Table 2

Ex. No.	Starting Material	Product NMR $\delta$
5	(III-5)	$I^{b-5}$ (X: O): ( $CDCl_3$ ) 1.27 (d, 6H, J = 6.6Hz); 1.35-1.68 (m, 2H); 2.47 (m, 2H); 3.34 (m, 1H); 3.78 (s, 3H); 4.03 (s, 3H); 4.19 (m, 1H); 4.43 (m, 1H); 5.43 (dd, 1H, J = 5.6, 16Hz); 6.59 (dd, 1H, J = 1.4, 16Hz); 7.03-7.64 (m, 4H) $I^{a-5}$ (X: O): Yield 57.7% ( $CDCl_3, CD_3OD$ ) 1.27 (d, 6H, J = 6.6Hz); 1.35-1.68 (m, 2H); 2.17 -2.43 (m, 2H); 3.36 (m, 2H); 4.05 (s, 3H); 4.3 7 (m, 2H); 5.48 (dd, 1H, J = 5.6, 16Hz); 6.54 (dd, 1H, J = 1.4, 16Hz); 7.06-7.65 (m, 4H)
6	(III-4)	$I^{b-6}$ (X: N- $SO_2NMe_2$ ): ( $CDCl_3$ ) 1.26 (d, 6H, J = 6.6Hz); 1.38-1.62 (m, 2H); 2.47 (d, 2H, J = 5.8); 2.84 (s, 6H); 3.35 (m, 1H); 3.64 (s, 3H); 3.74 (s, 3H); 4.20 (m, 1H); 4.44 (m, 1H); 5.42 (dd, 1H, J = 5.4, 16Hz); 6.60 (dd, 1H, J = 1.2, 16Hz); 7.03-7.64 (m, 4H) $I^{a-6}$ : Yield: 91.2% ( $CDCl_3, CD_3OD$ ) 1.26 (d, 6H, J = 6.6Hz); 1.36-1.69 (m, 2H); 2.15-2.50 (m, 2H); 2.85 (s, 6H); 3.41 (m, 2H); 3.6 4 (s, 3H); 4.04 (m, 1H); 4.37 (m, 1H); 5.48 (dd, 1H, J = 5.6, 16Hz); 6.54 (dd, 1H, J = 1, 16Hz); 7.05-7.66 (m, 4H)

Table 3

Ex. No.	Starting Material	Product NMR $\delta$
7	(III-6)	$I^{b-7}$ (X:N-NHSO <sub>2</sub> Me) : Yield:87.8% (CDCl <sub>3</sub> ) 1.24 (d, J=7,6H); 1.51 (m, 2H); 2.47 (d, J=6, 2H); 2.95 (s, 3H); 3.35 (hept, J=7,1H); 3.46 (d, J=2,1H); 3.55 (s, 3H); 3.66 (d, J=2,1H); 3.74 (s, 3H); 4.18 (m, 1H); 4.44 (m, 1H); 5.41 (dd, J=5,16, 1H); 6.58 (dd, J=2,16, 1H); 7.09 (m, 2H); 7.58 (m, 2H); 7.70 (s, 1H) $I^{a-7}$ (X:N-NHSO <sub>2</sub> Me) : Yield:74.7%(D <sub>2</sub> O) 1.23 (d, J=7,6H); 1.51 (m, 2H); 2.26 (d, J=6,2 H); 3.10 (s, 3H); 3.37 (hept, J=7,1H); 3.44 (s, 3H); 3.70 (m, 1H); 4.29 (q, J=6, 1H); 5.39 (dd, J=5,16, 1H); 6.58 (d, J=16, 1H); 7.19 (m, 2H); 7.52 (m, 2H)

### Example 7

#### Calcium salt of the compound ( $I^{a-1}$ )

The compound ( $I^{a-1}$ ) (sodium salt) 1.50 g (3.00 mmol) is dissolved in 15 ml of water and stirred at room temperature under a nitrogen atmosphere. Successively 3.00 ml (3.00 mmol) of 1 mol/L calcium chloride 3.00 ml (3.00 mmol) is added dropwise thereto over 3 minutes. The reaction mixture is stirred at the same temperature for 2 hours, and the resulting precipitate is collected, washed with water and dried to give 1.32 g of calcium salt as powder. This compound started to melt at a temperature of 155 °C, but the definitive melting point is ambiguous.  $[\alpha]_D^{25} = +6.3 \pm 0.2^\circ$  (C=2.011, 25.0 °C, MeOH)

Anal Calcd. (%) for C <sub>22</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> SF*0.5Ca*0.5H <sub>2</sub> O					
: C,51.85;	H,5.53;	N,8.25;	F,3.73;	Ca,3.93	
Found : C,51.65;	H,5.51;	N,8.47;	F,3.74;	Ca,4.07	

### Biological Activity

#### Experiment

##### The HMG-CoA reductase inhibitory effect

##### (1) Preparation of rat liver microsomes

Sprague-Dawley rats, which were in free access to ordinary diets containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsomes. The thus obtained microsomes were then purified according to the manner described by Kuroda et al., Biochem. Biophys. Act, 486, 70 (1977). The microsomal fraction obtained by centrifugation at 105000 × g was washed once with a buffered solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in a 100 mM potassium phosphate buffer, pH 7.4). It was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The thus obtained homogenate was cooled down and kept at -80 °C.

##### (2) Measurement of the HMG-CoA reductase inhibitory activities

The rat liver microsome sample (100  $\mu$ l), which was preserved at -80 °C, was fused at 0 °C and diluted with 0.7 ml of a cold potassium phosphate buffer (100 mM pH7.4). This was mixed with 0.8 ml of 50 mM EDTA (buffered with the aforementioned potassium phosphate buffer) and 0.4 ml of 100 mM dithiothreitol solution (buffered with the aforementioned potassium phosphate buffer), and the mixture was kept at 0 °C. The microsome solution (1.675 ml) was mixed with 670  $\mu$ l of 25 mM NADPH (buffered with the aforementioned potassium phosphate buffer), and the solution was added to the solution of 0.5mM [<sup>3</sup>-<sup>14</sup>C]HMG-CoA (3mCi/mmol). A solution (5  $\mu$ l) of sodium salt of the test compound dissolved in potassium

phosphate buffer was added to 45  $\mu$  l of the mixture. The resulting mixture was incubated at 37 °C for 30 minutes and cooled. After termination of the reaction by addition of 10  $\mu$  l of 2N-HCl, the mixture was incubated again at 37 °C for 15 minutes and then 30  $\mu$  l of this mixture was applied to thin-layer chromatography on silica gel of 0.5 mm in thickness (Merck AG, Art 5744). The chromatograms were developed in toluene/acetone (1/1) and the spot, whose Rf value was between 0.45 to 0.60, were scraped. The obtained products were put into a vial containing 10 ml of scintillator to measure specific radio-activity with a scintillation counter. The activities of the present compounds are shown in Table 4 as comparative data, based on the assumption that the activity of mevinolin (sodium salt) as the reference drug is 100.

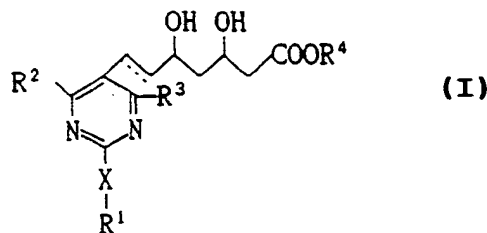
Table 4

Test Compound	HMG-CoA reductase inhibitory activities
a-1	442
a-3	385
a-5	279
a-7	260
Mevinolin Na	100

The test data demonstrates that the compounds of the present invention exhibit HMG-CoA reductase inhibition activities superior to mevinolin.

### Claims

1. A compound represented by the formula (I):



wherein R<sup>1</sup> is lower alkyl, aryl, or aralkyl, each of which may have one or more substituents; R<sup>2</sup> and R<sup>3</sup> each is independently hydrogen, lower alkyl, or aryl, and each of said lower alkyl and aryl may have one or more substituents; R<sup>4</sup> is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a substituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone.

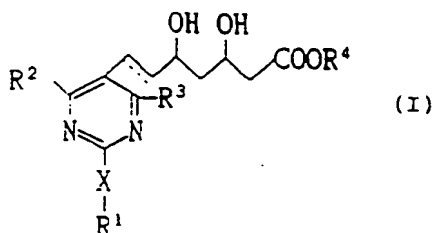
2. The compound claimed in claim 1, wherein X is sulfur.
3. The compound claimed in claim 1, wherein X is oxygen.
4. The compound claimed in claim 1, wherein X is sulfonyl.
5. The compound claimed in claim 1, wherein X is imino which may have a substituent.
6. The compound claimed in claim 5, wherein the substituent is acyl, alkylsulfonylamino, or alkylsulfonyl.
7. The compound claimed in claim 1, wherein said compound takes an optically active form.
8. A pharmaceutical composition comprising the compound claimed in any one of claims 1 to 7 as an

active ingredient.

9. A pharmaceutical composition according to claim 8 which is useful as an HMG-CoA reductase inhibitor.

5 **Claims for the following Contracting State : GR**

1. A compound represented by the formula ( I ):



20 wherein R<sup>1</sup> is lower alkyl, aryl, or aralkyl, each of which may have one or more substituents; R<sup>2</sup> and R<sup>3</sup> each is independently hydrogen, lower alkyl, or aryl, and each of said lower alkyl and aryl may have one or more substituents; R<sup>4</sup> is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a substituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone.

25 2. The compound claimed in claim 1, wherein X is sulfur.

3. The compound claimed in claim 1, wherein X is oxygen.

30 4. The compound claimed in claim 1, wherein X is sulfonyl.

5. The compound claimed in claim 1, wherein X is imino which may have a substituent.

35 6. The compound claimed in claim 5, wherein the substituent is acyl, alkylsulfonylamino, or alkylsulfonyl.

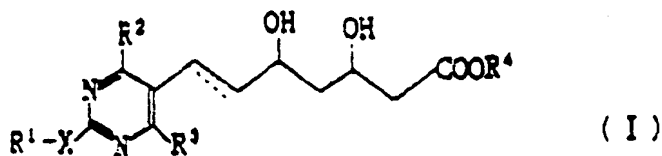
7. The compound claimed in claim 1, wherein said compound takes an optically active form.

40 8. A process for the preparation of a pharmaceutical composition containing as active ingredient a compound as defined in any one of claims 1 to 7 which comprises admixing the compound with a pharmaceutically acceptable carrier.

9. A process according to claim 8 wherein the pharmaceutical composition prepared is useful as an HMG-CoA inhibitor.

45 **Claims for the following Contracting State : ES**

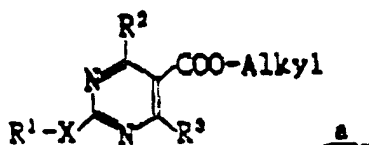
1. A process for the preparation of a compound of the formula ( I ):



wherein R<sup>1</sup> is lower alkyl, aryl, or aralkyl, each of which may have one or more substituents; R<sup>2</sup> and R<sup>3</sup> each is independently hydrogen, lower alkyl, or aryl, and each of said lower alkyl and aryl may have

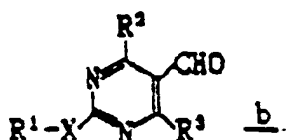
one or more substituents;  $R^4$  is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a substituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone,

(1) which comprises subjecting the compound a of the formula:



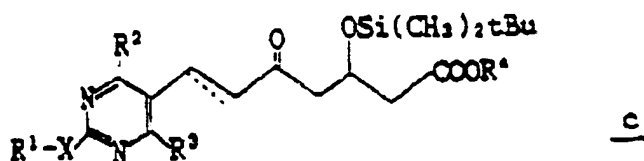
wherein  $R^1$ ,  $R^2$ , and  $R^3$  each have the same meaning as defined above, and Alkyl means lower alkyl, to a reduction in an appropriate inactive solvent in the presence of a reductant to give the alcohol compound,

(2) subjecting the thus obtained alcohol compound to an oxidation in an appropriate solvent in the presence of an oxidizing agent to give aldehyde compound b of the formula:



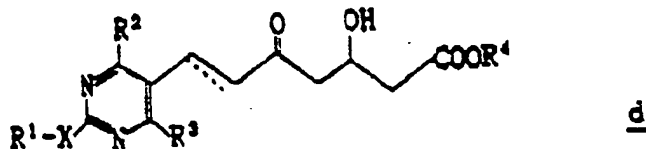
wherein  $R^1$ ,  $R^2$ , and  $R^3$  each have the same meaning as defined above,

(3) which is reacted with 3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanoic acid derivatives in an appropriate solvent to give the compound c of the formula:



wherein the dotted line denotes the presence or absence of the double bond,  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  each have the same meaning as defined above,

(4) which is subjected to elimination of the tert-butyldimethylsilyl group in an appropriate organic solvent in the presence of a hydrogen halogenide to give the compound d of the formula:



wherein the dotted line,  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  each have the same meaning as defined above,

(5) which is reacted with diethylmethoxyborane and  $\text{NaBH}_4$  in an alcohol-organic solvent mixture and subjected to column chromatography on silica gel to give the compound (I) (in the case where  $R^4$  is lower alkyl), or the obtained compound (I) may be subjected to saponification in a polar solvent with a solution of metallic hydroxide ( $R^4$  : cation), or after the saponification, it is neutralized with an inorganic acid and extracted with an organic solvent ( $R^4$  : hydrogen).



2. The process according to claim 1 wherein in the compound prepared X is sulfur.
3. The process according to claim 1 wherein in the compound prepared X is oxygen.
- 5 4. The process according to claim 1 wherein in the compound prepared X is sulfonyl.
5. The process according to claim 1 wherein in the compound prepared X is imino which may have a substituent.
- 10 6. The process according to claim 5 wherein the substituent is acyl, alkylsulfonylamino or alkylsulfonyl.
7. The process according to claim 1 wherein the compound prepared takes an optically active form.
8. A process for the preparation of a pharmaceutical composition containing as active ingredient a  
15 compound as defined in any one of claims 1 to 7 which comprises admixing the compound with a pharmaceutically acceptable carrier.
9. A process according to claim 8 wherein the pharmaceutical composition prepared is useful as an HMG-CoA inhibitor.

20

25

30

35

40

45

50

55



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 92 11 1090

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 367 895 (SANDOZ) * claims *  -----	1,7-9	C07D239/42 C07D239/38 A61K31/505
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 05 OCTOBER 1992	Examiner FRANCOIS J.C.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document  T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons  & : member of the same patent family, corresponding document			

EP FORM 1500 (11.92) (P.0001)